〈表3〉悪性関節リウマチ（MRA）の改訂診断基準

既存の関節リウマチ（RA）に血管炎をはじめとする関節外症状を認め，難治性もしくは重篤な臨床病態を伴う場合，これを悪性関節リウマチ（malignant rheumatoid arthritis：MRA）と定義し，以下の基準により診断する

A. 臨床症状，検査所見

1. 多発性神経炎
   知覚障害，運動障害いずれを伴ってもよい
2. 皮膚潰瘍または梗塞または指趾壊疽
   感染や外傷によるものは含まない
3. 皮下結節
   骨突起部，伸側表面もしくは関節近傍にみられる皮下結節
4. 上強膜炎または虹彩炎
   眼科的に確認され，他の原因によるものは含まない
5. 滲出性胸膜炎または心嚢炎
   感染症など，他の原因によるものは含まない。癒着のみの所見は陽性にとらない
6. 心筋炎
   臨床所見，炎症反応，筋原性酵素，心電図，心エコーなどにより診断されたものを陽性とする
7. 間質性肺炎または肺線維症
   理学的所見，胸部X線，肺機能検査により確認されたものとし，病変の広がりは問わない
8. 臓器梗塞
   血管炎による虚血，壊死に起因した腸管，心筋，肺などの臓器梗塞
9. リウマトイド因子高値
   2回以上の検査で，RAHAテスト2560倍以上（RF定量テストにて960IU／mL以上）の高値を示すこと
10. 血清低補体価または血中免疫複合体陽性
    2回以上の検査で，C3，C4などの血清補体成分の低下またはCH50による補体活性化の低下をみること。または2回以上の検査で血中免疫複合体陽性（C1q結合能を基準とする）をみること（ただし，医療保険が適用されていないので検査のできる施設に限る）

B. 組織所見

皮膚，筋，神経，その他の臓器の生検により，小ないし中動脈に壊死性血管炎，肉芽腫性血管炎ないしは閉塞性内膜炎を認めること

判 定

1987年の米国リウマチ学会の関節リウマチの診断基準を満たし，上記に挙げる項目のなかで，(1) Aの3項目以上満たすもの，または，(2) Aの1項目以上とBの項目があるもの，をMRAと診断する

鑑別疾患：感染症，アミロイドーシス，Felty症候群，全身性エリテマトーデス，多発性筋炎，MCTDなど

（厚生省（現厚生労働省）系統的脈管障害調査研究班 1987年度研究報告書．P189-191より）

2）免疫抑制薬

ステロイド無効例，ステロイド有効だが減量・離脱が困難な例，副作用でステロイド継続困難な例などでは，免疫抑制薬の適応となる。アザチオプリン，シクロホスファミド，またはミゾリビン内服，シクロホスファミド間欠静注療法を行う。間質性肺炎を認めない例ではメトトレキサート間欠療法などを行う。

RAに伴う単神経炎にエタネルセプトが有効であったという報告もあるが，MRAにおける生物学的製剤の有用性は今後検討を要する。

3）抗凝固療法，抗血小板薬，血管拡張薬

皮膚梗塞，潰瘍，臓器虚血・梗塞に対して，ワルファリンカリウムなどの抗凝固薬，アスピリンなどの抗血小板薬，ベラプロストナトリウムなどの血管拡張薬を併用する。

4）血漿交換療法

ステロイドをはじめとする免疫抑制療法で十分な効果が認められず，免疫複合体高値，クリオグロブリン血症，過粘稠度症候群などの病態への関与が疑われる場合には，IgGリウマトイド因子や免疫複合体などの液性因子を除去する目的で，血漿交換療法を行う。

◉ 処方例：臓器虚血・梗塞の場合

1) プレドニゾロン（プレドニン5mg） 8～12錠/日 1日3～4回（毎食後，就寝前）
2) ベラプロストナトリウム（プロサイリン20μg） 6錠/日 1日3回（毎食後）
3) アスピリン（バイアスピリン100mg） 1錠/日 1日1回（朝食後）

■副作用と対策

ステロイド大量療法や免疫抑制療法による易感染状態により，カリニ肺炎やサイトメガロウイルス（CMV）感染症などを併発することがあり，注意を要する。ST合剤によるカリニ肺炎の一次予防を行い，β-D-グルカン，CMVアンチゲネミアのモニタリングにより，早期発見につとめる。

コントロールがうまくいかないとき

原因 ①間質性肺炎，②皮膚潰瘍

対応 ①メトトレキサート，ブシラミン，金剤などにより間質性肺炎がみられることがあり，これらの薬剤を中止する。DMARDsは，サラゾスルファピリジン，ミゾリビンへ変更する。

②難治性皮膚潰瘍では，経口血管拡張薬から，リポPGE_1または抗トロンビン薬の点滴静注へ変更する。

◎薬物療法の実際

45 治療戦略 バリエーション②：回帰性リウマチと思われるケース

■ポイント

◉再発性の急性関節炎と関節周囲炎。
◉発作は数日から1週間程度で消失し，発作と発作の間には無症状の期間が数日から数カ月ある。
◉関節リウマチ（RA）への移行が30～40％でみられる。
◉注射金剤の効果が報告されている。

■定義，概念

1944年にHenchおよびRosenbergが，再発性の急性関節炎と関節周囲炎で，発作は数日から1週間程度で消失し，発作と発作の間には無症状の期間（間欠期）が数日から数カ月ある稀な疾患として，回帰性リウマチ（palindromic rheumatism）を記載した（*Arch Intern Med* 73：292-321, 1944）。RAへの移行が30～40％でみられる。

■病因，疫学

回帰性リウマチからRAへの移行がみられることを除き，本症候群の病因や成因はほとんど明らかでない。男女比はほぼ同数で，年齢は20～60歳とされる。回帰性リウマチの有病率はRAのほぼ1／10とされる。

〈表1〉回帰性リウマチの発作時の関節障害の分布

		患者（%）	
		平均	範囲
障害関節	MPおよびPIP	91	74～100
	手首	78	54～82
	膝	64	41～94
	肩	65	33～75
	足首	50	10～67
	足	43	15～73
	肘	38	13～60
	腰	17	0～40
	顎関節	8	0～28
	脊椎	4	0～11
	胸鎖関節	2	0～6
	傍関節部位	27	20～29

（Guerne PA, *et al*：*Am J Med* 93：451-460, 1992より改変）

■症　状

発作はどの関節にも起こり得るが，手関節，手指関節，膝関節，肩関節，足関節が侵されることが多い。脊椎や顎関節は稀である（表1）。発作は，突然に1～2関節に起こり，数時間で疼痛は最大となる。それとともに，罹患関節の表面または周囲に，著明な発赤，熱感，腫脹を認める。発作は，非常に短期間で（多くは48時間以内），1週間以内に消失する。時に数時間で消失することもある。発作の頻度は，毎日から毎月まで様々である。発熱を伴う場合もある。また，発作とともに一過性に皮下結節がみられることもある。回帰性リウマチの長期経過は不明な点も多いが，自然寛解は10％以下で，多くの例では破壊性関節炎を伴わず周期的に発作を認める。30～40％の患者では，発作の程度は軽くなるが回数が頻繁になり，複数関節を同時に罹患しRAへ移行する。

■検　査

発作時には，赤沈亢進や炎症反応上昇を認めるが，間欠期にはこれらの異常を認めない。リウマトイド因子の陽性頻度は30～60％とされ，陽性患者では発作が重症でRAへ移行しやすいとの報告やRAへの移行期にリウマトイド因子が陽性化するとの報告もある（Hannonen P：*Scand J Rheumatol* 16：413-420, 1987）。リウマトイド因子以外の自己抗体では，抗CCP抗体と抗ケラチン抗体が調べられている。抗CCP抗体の陽性率および抗体価はRAと同様だが，抗ケラチン抗体の頻度はRAに比して低い。さらに，RAと同様に，リウマトイド因子と抗CCP抗体には，相関がみられた。こうした成績から，回帰性リ

〈表2〉再発性または反復性の関節炎を認める疾患

◎結晶性関節炎	◎Whipple病
◎反応性関節炎	◎全身性自己免疫疾患
◎炎症性腸疾患に伴う関節炎	家族性地中海熱
◎回帰性リウマチ	TRAPS症候群
◎ベーチェット病	高IgD症候群
◎サルコイドーシス	◎高脂血症
◎再発性多発軟骨炎	◎間欠性関節水腫

ウマチをRAの亜型と推定する報告もある（Salvador G：*Rheumatology* 42：972-975, 2003）。

回帰性リウマチは家族性に発症することがあるが，HLA-DR4およびDR1との強い相関は認められていない。

関節液検査では，非特異的，亜急性の炎症反応を認める。X線検査では，発作中に軟部組織の腫脹を認めるほかは，正常である。滑膜生検では，微小血管傷害を認める。

■診断および鑑別診断

診断は，再発性の急性関節炎と関節周囲炎という特徴的な臨床所見に基づいて行われる。再発性または反復性の関節炎を認める疾患を鑑別する必要がある（**表2**）。

■薬物治療の考え方

NSAIDsにより症状の軽減はみられるものの，十分な効果が得られないことも多い。ステロイドやコルヒチンを定期的に服用しても，発作を予防することは困難である。DMARDsの効果は明らかでないが，注射金剤で最も一定した効果が報告されている（Mattingly S：*Ann Rheum Dis* 25：307-317, 1966）。ペニシラミンおよびサラゾスルファピリジンも試みられている。欧米ではクロロキンも試されているが，本邦では承認されていない。メトトレキサートおよびレフルノミドの使用報告はこれまでない。

◆処方例◆

◎処方例①：発作時および間欠時〈併用〉

1) ジクロフェナク（ボルタレン25mg）3錠/日 1日3回（毎食後）
2) 金チオリンゴ酸ナトリウム（シオゾール注25mg）1A/日 1月1回筋注

◎処方例②：発作時および間欠時〈併用〉

1) ジクロフェナク（ボルタレン25mg）3錠/日 1日3回（毎食後）
2) ブシラミン（リマチル 100mg*）3錠/日 1日3回（毎食後）

＊50mg錠もあるので注意（☞*§19*, 58頁 表1）

◎処方例③：発作時および間欠時〈併用〉

1) ジクロフェナク（ボルタレン25mg）3錠/日 1日3回（毎食後）
2) サラゾスルファピリジン（アザルフィジンEN 500mg*） 2錠/日 1日2回（朝・夕食後）

＊250mg錠もあるので注意（☞*§19*, 58頁 表1）

◎処方例④：関節炎および関節周囲炎が強い場合
〈いずれかを用いる。併用可〉

1) ファルネシル酸プレドニゾロン（ファルネラートゲル1.4%） 1日数回外用
2) フェルビナク（セルタッチパップ） 1日2回患部貼付

コントロールがうまくいかないとき

原因 ①発作の頻度が多い。②発作の程度は軽くなるが回数が頻繁になる。

対応 ①激しい運動や感染が発作の誘因となることがあり，生活指導を行う。
②RAへの移行を疑い，RAに準じたDMARDs療法を行う。

46 治療戦略 バリエーション③:Felty症候群

■ポイント

- ◉関節リウマチ(RA)と同様の関節症状に脾腫と白血球減少を伴うもの。
- ◉関節炎は高度の骨破壊を伴うことが多い。
- ◉関節外症状として,リウマトイド結節,リンパ節腫脹,下腿潰瘍,末梢神経障害などを合併する。
- ◉関節炎および関節外症状を抑え,白血球減少による感染症を管理することが治療上重要である。

■定義,概念

1924年にFeltyがRA患者に脾腫と白血球減少を伴う5例を報告した(Felty AR:*Bull Johns Hopkins Hosp* 35:16-20, 1924)。この三徴候を伴うものはFelty症候群と呼ばれ,RAの一亜型と考えられる。

■病因,疫学

本症候群の病因は明らかでない。RAの家族歴をもつことが多く,HLA-DR4との相関が高いことより,発症に遺伝的素因の関与が推定される。白血球減少症は好中球減少による。その機序として以前は脾機能亢進が考えられていたが,現在では顆粒球特異的抗核抗体などの自己抗体や免疫複合体が好中球寿命を短縮する可能性や血漿中の液性因子や細胞性因子が骨髄増殖能を抑制する可能性が指摘されている。

欧米に比べて本邦での本症候群の発症頻度は少なく,RAの約1%とされる。男女比は1:2～4と女性に多く,年齢は50～70歳とRAに比して高齢である。

〈表1〉Felty症候群の関節外症状

リウマトイド結節	76%
体重減少	68%
シェーグレン症候群	56%
リンパ節腫脹	34%
下腿潰瘍	25%
胸膜炎	19%
皮膚色素沈着	17%
神経障害	17%
上強膜炎	8%

(Pinals RS, *et al*: *Textbook of Rheumatology*. 5th ed, 1997, p951-954より)

■症　状

RAと同様の関節症状に加えて,全身症状(発熱,全身倦怠感,体重減少),血管炎による症状(胸膜炎,肺線維症,心膜炎,末梢神経炎,上強膜炎,皮膚潰瘍),脾腫などがみられる。RAに比べ皮下結節,肝腫大,シェーグレン症候群の合併頻度も高い(**表1**)。好中球減少による感染症を繰り返す。

■検　査

1) 血球障害

白血球数減少は,好中球減少によるものであり,好中球数は2000/μL未満と定義される。好中球減少の程度は,経過中変動し,自然寛解することもある。貧血は,RAと同様の慢性炎症パターンを示すが,溶血性貧血を示すこともある。しばしば血小板減少を合併する。

2) 免疫異常

RAに比してリウマトイド因子の陽性頻度は高い(95～100%)。IgM型RFに加え,IgG型およびIgA型リウマトイド因子も認める。抗核抗体の陽性率は高い(47～100%)。抗ヒストン抗体も高率で(68～83%),抗ssDNA抗体がしばしば陽性となるが,抗dsDNA抗体は稀である。免疫複合体の陽性率が高く,補体は低値を示す。顆粒球特異的抗核抗体や抗白血球細胞膜抗体が陽性

〈表2〉Felty症候群とRAを合併したLGL症候群の臨床的特徴

	Felty症候群	RA合併LGL症候群
びらん性関節炎	多い	稀
関節外症状	多い	稀
関節炎と好中球減少の発症	しばしば同時	先行
脾　腫	多い	多い
易感染性	多い	稀
白血球数	減少	正常
リンパ球増加	なし	あり
CD4：CD8比	正常	低下
TCR遺伝子異常	なし	あり
白血病への進展	稀	3～14％
リウマトイド因子陽性	多い	多い
抗核抗体陽性	多い	多い
抗顆粒球抗体	多い	多い
脾摘に対する反応性	良好	再燃あり

(Balint GP, *et al*：*Best Practice & Research Clinical Rheumatology* 18：631-645, 2004より改変)

となるとの報告もある。蛍光抗体法で抗好中球細胞質抗体が高率に陽性パターンを示し，その対応抗原はラクトフェリンGなど非特異的ANCAである。

3）その他

RAと同様に赤沈亢進，CRP上昇，高ガンマグロブリン血症を認める。

■診断および鑑別診断

長期に（通常は10年以上）RAに罹患した患者で，原因不明の持続的な好中球減少，脾腫を認めた場合に本症候群と診断する。悪性関節リウマチ，RAと全身性エリテマトーデスの重複例，RAとシェーグレン症候群の重複例，RAに肝硬変や薬剤性好中球減少を合併した場合，重症感染症を合併した場合などを鑑別する必要がある。

末梢血中に巨大顆粒リンパ球（LGL）の出現を認め，好中球減少と脾腫を特徴とするLGL症候群と呼ばれる疾患では，高率に（20～30％）RAを合併することから，Felty症候群との鑑別が問題となる（表2）。

■薬物治療の考え方

関節炎および関節外症状を抑え，白血球減少による感染症を管理することが重要である。

1）関節炎および関節外症状に対する治療

RAの治療に準じ治療する。すなわち，NSAIDsを投与し，DMARDsを併用する。疾患活動性の低下により白血球数の回復も期待される。一方で，NSAIDsおよびDMARDsによる好中球減少の副作用に注意を要する。

DMARDsとして，金製剤，サラゾスルファピリジン（アザルフィジンEN）またはブシラミン（リマチル）を選択する。血管炎症状に対してはステロイドを投与する。

2）白血球減少に対する治療

有効な治療法は確立されていない。ステロイド，炭酸リチウム，ステロイドパルス療法，免疫抑制薬，G-CSF，ガンマグロブリン大量療法，血漿交換療法の有用性が報告されている。薬物治療が無効で感染症を繰り返す例では脾摘も試みられ（Coon WW, *et al*：*Am J Surg* 149：272-275, 1985），80％の例で白血球が回復したとの報告がある一方で，こうした効果は一時的であるとの報告もある。

3）感染症の治療

好中球数1000／μL以下では感染症発症のリスクは高い。抗菌薬により感染症をコントロールする。

◆処方例◆

◉処方例①：関節炎の場合〈併用〉

1) ロキソプロフェン（ロキソニン60mg）　3錠/日　1日3回（毎食後）

2) サラゾスルファピリジン（アザルフィジンEN 500mg*）　2錠/日 1日2回（朝・夕食後）

＊250mg錠もあるので注意（☞§19, 58頁 表1）

◉処方例②：血管炎の場合

・プレドニゾロン（プレドニン5mg）　6錠/日 1日3回（朝・夕食後）

■予　後

感染症の合併頻度が高く，予後不良である。

コントロールがうまくいかないとき

原　因　①DMARDsが無効，②易感染性

対　応　①関節炎および白血球減少にメトトレキサートの有効性を示す成績が欧米で示されている。骨髄抑制に注意して単独で，またはステロイドとの併用で慎重に投与する。

②好中球数減少，好中球機能低下など原病によるもののほか，治療に用いたステロイド，免疫抑制薬の影響による場合もあり，減量を考慮する。

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CASE REPORT

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Sensorimotor polyneuropathy as an initial clinical manifestation of sarcoidosis

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Abstract A 45 year-old Japanese woman developed numbness and tingling of both hands and feet. Electrophysiological examination revealed sensorimotor polyneuropathy. She was diagnosed as suffering from sarcoidosis on the basis of the pathological findings from dermal biopsy. Steroid therapy effectively improved the clinical symptoms. Although sarcoid neuropathy is rare, this case suggests sensorimotor polyneuropathy is an important symptom of sarcoidosis and can represent the initial clinical manifestation of the disease.

Key words Axonal degeneration · Electromyography (EMG) · Sarcoidosis · Sensorimotor polyneuropathy

Introduction

Sarcoidosis is a disorder of unknown cause, which affects multiple organs with formation of granulomatous lesions and causes many different clinical manifestations including neurological signs. Among its various manifestations, sarcoid neuropathy is a rare complication of sarcoidosis. Here, we report a Japanese patient with sarcoidosis who showed progressive gait disturbance due to sensorimotor polyneuropathy.

Case report

A 45-year-old Japanese woman developed numbness and tingling of both hands and feet in March 2000. Magnetic resonance imaging of the spine was performed at another hospital and no major abnormality was observed. In April, she began to have painful legs with difficulty in walking. She was referred to our outpatient clinic for further examination in June 2000. At the time of admission, she had fever at 37°C and had pain in her lower extremities. She was a housewife with no alcohol habit and had never been exposed to any toxic chemical materials. On physical examination, there was slight edematous erythema in her feet. However, there was no facial erythema, xerostomia, scleroderma, muscle atrophy, or subcutaneous nodules. Neurological examination revealed symmetric muscle weakness in the plantar extensors and flexors, iliopsoas, hamstrings, and gastrocnemius muscles graded as 3–4/5, as well as painful paresthesia. Cutaneous sensation was impaired in glove and stocking distribution to the ankles and wrists. Brachioradialis and Achilles tendon reflexes were absent. However, there were no cranial nerve abnormalities.

Laboratory findings (Table 1) showed an erythrocyte sedimentation rate (ESR) of 39 mm/h; there was a normal urinalysis and blood count with no eosinophilia. Liver and renal functions were normal. The serum creatine kinase, calcium, vitamin B_{12}, and folic acid values were within the normal range. Serum angiotensin-converting enzyme (ACE) was 23.6 IU/l (normal 7.7–29.4 IU/l), but lysozyme was elevated to 12.5 μg/ml (normal 4.2–11.5 μg/ml). Hypergammaglobulinemia was found and C-reactive protein was slightly elevated to 0.24 mg/dl. Cryoglobulin, antineutrophil cytoplasmic autoantibodies (PR-3 ANCA, MPO-ANCA), and immune complexes were within normal limits. Anti-dsDNA, anti-SS-A, anti-SS-B, anti-RNP, anti-Jo-1 antibodies, and the tuberculin skin test were all negative.

In nerve conduction studies in June 2000 (Table 2), distal motor latencies were prolonged in the median and ulnar nerves. Compound muscle action potentials (CMAPs) were very low in amplitude in the tibial and peroneal nerves, and temporal dispersion and conduction block were not detected. Sensory nerve action potentials (SNAPs) of the median nerve were also low in amplitude. However, motor and sensory conduction velocities were relatively preserved

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Table 1. Laboratory data on admission

ESR	39 mm/h	Blood chemistry		Immunological	
Urinalysis		TP	7.0 g/dl	IgG	1880 mg/dl
Protein	(–)	Alb	3.6 g/dl	IgA	501 mg/dl
Sugar	(–)	BUN	12.3 mg/dl	IgM	245 mg/dl
Cast	(–)	Cre	0.6 mg/dl	CRP	0.24 mg/dl
CBC		Ca	9.2 mg/dl	C3	65 mg/dl
WBC	4400/μl	IP	3.1 mg/dl	C4	17 mg/dl
	(Band+Seg 65, Lymph 20, Mono 9, Eosino 5, Baso 1)	LDH	218 IU/l	IC (Anti-C3d)	11.8 μg/ml
RBC	4.02×10^6/μl	ALT	36 IU/l	RF	<10 IU/ml
Hb	12.2 g/dl	AST	31 IU/l	ANA	(–)
Ht	37.2 %	CK	48 IU/l	Cryoglobulin	(–)
Plt	25.2×10^4/μl	FBS	91 mg/dl	PR3-ANCA	(–)
		ACE	23.6 IU/l	MPO-ANCA	(–)
		Lysozyme	12.5 μg/ml	Anti-dsDNA	(–)
		Vitamin B_{12}	1090 pg/dl (233–914)	Anti-U1RNP	(–)
				Anti-SSA	(–)
				Anti-SSB	(–)
				Anti-Jo-1	(–)

IC, immune complex

Table 2. Nerve conduction studies

	June 2000	January 2001	January 2003
Median nerve (rt)			
DLT (ms)	6.8	4.2	4.7
CMAP (mV)	4.0	9.9	13.4
MCV (m/s)	50.0	48.7	47.3
SNAP(μV)	12	18	49
SCV (m/s)	29.2	42.4	42.4
Ulnar nerve (rt)			
DLT (ms)	5.2	3.7	4.4
CMAP (mV)	7.0	17	18
MCV (m/s)	52.5	52.5	48.6
Tibial nerve (rt)			
DLT (ms)	N.E.	5.1	4.1
CMAP (mV)	N.E.	4.0	15.2
MCV (m/s)	N.E.	38.6	43.7
Peroneal nerve (rt)			
DLT (ms)	5.3	4.8	5.4
CMAP (mV)	0.2	–	64
MCV (m/s)	42.8	40.7	41.7

DLT, distal latency time; CMAP, compound muscle action potential; MCV, motor conduction velocity; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; N.E., not evoked

in all nerves tested. In needle electromyography, denervation potentials were observed in the distal muscles. These findings were compatible with sensorimotor polyneuropathy due to axonal degeneration rather than segmental demyelination.

Slit-lamp biomicroscopy revealed that the patient had uveitis. Swelling of bilateral hilar lymph nodes was observed by chest computed tomography (Fig. 1), and gallium scintigraphy disclosed abnormal uptake of bilateral hilar lymph nodes that was consistent with the finding of active sarcoidosis. The dermal biopsy of leg erythema showed non-caseating granuloma with infiltration of lymphocytes and a few giant cells, but no eosinophils (Fig. 2). Diseases possibly causing peripheral neuropathy due to axonal

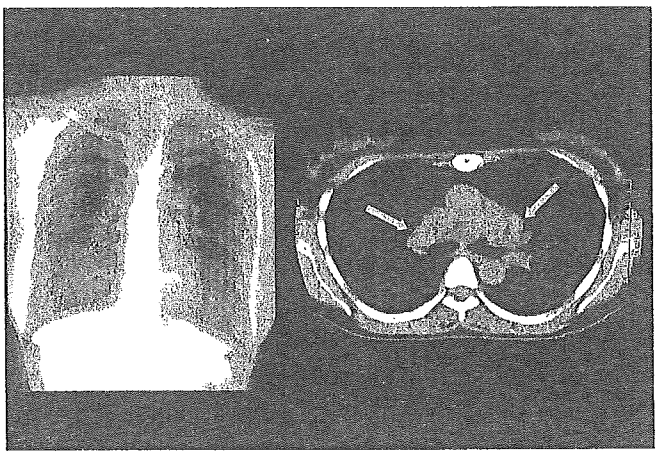

Fig. 1. Chest computed tomography findings on admission. Bilateral hilar lymphadenopathy was present (*arrows*)

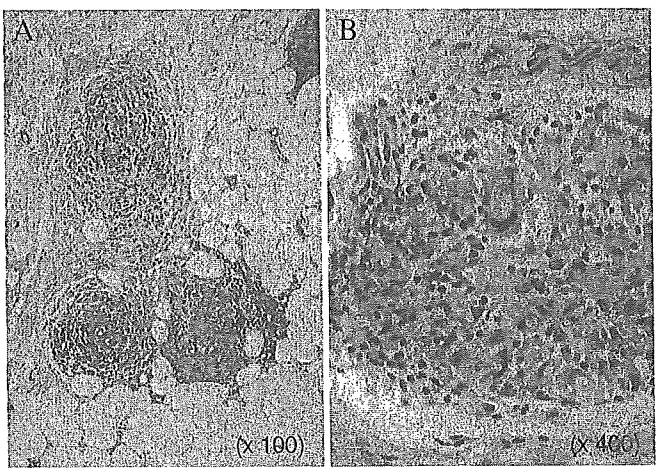

Fig. 2A,B. Histological sections of the erythematous dermal biopsy specimen (H&E staining; **A** ×100, **B** ×400). In higher magnification, non-caseating granuloma with infiltrating lymphocytes and a few giant cells are noted

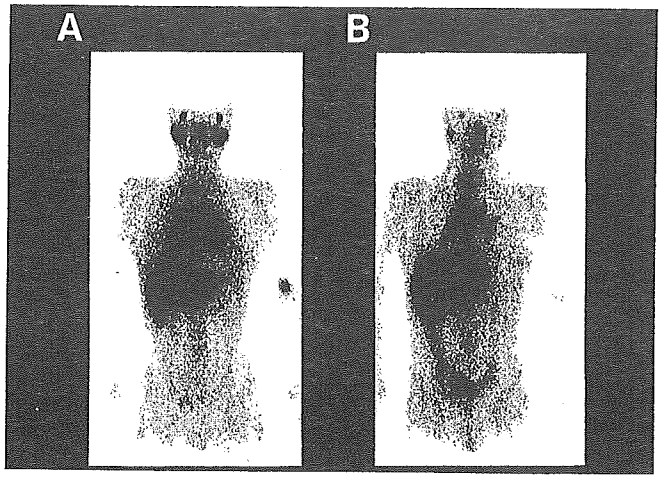

Fig. 3. Gallium scintigraphy of the whole body before (**A**) and after (**B**) steroid treatment. Abnormal uptake in the bilateral hilum improved markedly after treatment

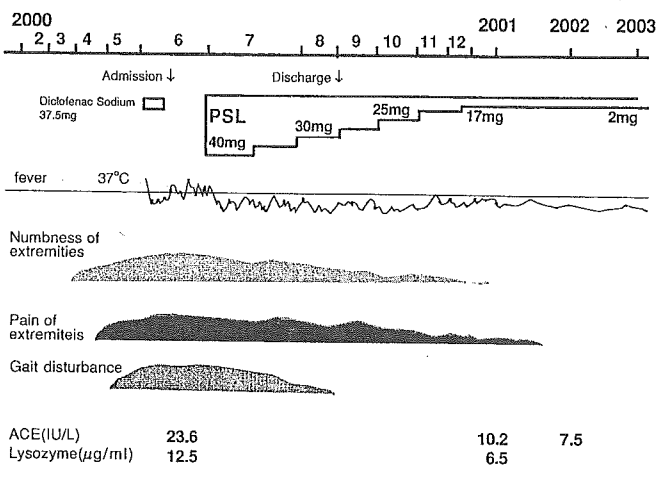

Fig. 4. Clinical course of this case. After prednisolone (*PSL*) treatment, numbness and pain of the extremities and gait disturbance were improved. Serum levels of angiotensin-converting enzyme (*ACE*) and lysozyme were also decreased

degeneration, such as metabolic diseases, toxic diseases, chronic inflammatory demyelinating polyneuropathy, infectious diseases, Vitamin B_{12} deficiency, and other collagen diseases, were all absent.

In July 2000, the diagnosis of sarcoidosis was made and the patient was started on 40mg daily of prednisolone (PSL), resulting in partial improvement of numbness and painful difficulty in walking. The following nerve conduction studies in January 2001 and January 2003 showed a marked improvement in CMAPs in the median, ulnar, tibial, and peroneal nerves, and SNAPs in the median nerve (Table 2). Abnormal uptake in the bilateral hilum also improved greatly after treatment (Fig. 3). Although the PSL dose was tapered gradually, her symptoms of peripheral neuropathies have been well controlled for 3 years. She continued to take the low dose of PSL (2mg daily) with no severe adverse events (Fig. 4).

Discussion

This is a case of sarcoidosis that showed sensorimotor polyneuropathy as an initial clinical manifestation. Neurological involvement in sarcoidosis has been reported to occur in 5%–15% of cases.[1,2] Moreover, in the context of neurological involvement, the prevalence of peripheral neuropathy including cranial nerve abnormality is estimated to occur in 4%–14% of cases,[3] although a recent study reported a higher incidence of peripheral nerve involvement.[4]

Previous studies have reported similar cases of sarcoidosis indicating spinal peripheral neuropathy (Table 3).[5–13] Of these, clinical features of 16 cases, including ours, are available for comparison. Ten of these 16 patients (63%) presented with peripheral neuropathy associated with sarcoidosis as an initial manifestation.[5–10,13] Thirteen (81%) cases had pulmonary symptoms during their course.[5,7–9,11–13] All patients were given corticosteroid therapy with improvement of their symptoms with only one exception. The patterns of neuropathy were variable, as seen in the previous studies.[4,6] Eight of 16 (50%) had sensorimotor polyneuropathy, four (25%) multifocal sensorimotor neuropathy, three (19%) multifocal sensory neuropathy, and one (6%) multifocal motor neuropathy.

The previous reports[1,6,7,11,12] indicated that sarcoidosis could elicit both compressive neuropathy due to perineural granuloma formation and ischemic neuropathy due to periangitis. Typically, complete compression causes Wallerian degeneration followed by demyelination, while vasculitis induces segmental demyelination first because Schwann cells are more vulnerable to ischemia. Although we did not perform sural nerve biopsy, the electrophysiological findings suggested that the main mechanism involved in this case was axonal degeneration. It is likely that sarcoid nodules observed in the specimen of skin biopsy compress the myelinated and unmyelinated neural fibers. Moreover, granulomatous vasculitis or vessel occlusion due to granulomas might also be involved in the neurological manifestations. In general, neuropathies due to vasculitis indicate mononeuritis multiplex. However, symmetrical polyneuropathy was also seen in previous reports.[5–7,14] Our case suggested symmetrical sensorimotor polyneuropathy. This might have been due to the severity and duration of the disease or the effects of systemic inflammation causing vasculitis.

We were able to perform nerve conduction tests before and after treatment. The electrophysiological parameters showed improvement after treatment. This suggests that nerve conduction studies are useful for evaluating the efficacy of treatment even when marked improvement of physiological symptoms is not seen.

Corticosteroid therapy is recommended for the peripheral neuropathy of sarcoidosis and is effective in most patients, although a placebo-controlled double-blind trial has not been performed. The improvement of electrophysiological parameters might be a consequence of the decreased ischemia due to vasculitis as well as reduction of

Table 3. Clinical manifestation of published neurosarcoidosis only manifesting the spinal peripheral neuropathy

First author/year[Ref.]	Age (years)/ sex	Initial manifestation	Pattern of neuropathy	Other symptoms	Therapy	Efficacy of PSL
Oh/1979[5]	58/F	Peripheral nerve	Sensorimotor polyneuropathy	Lung	100 mg	(+)
Nemni/1981[6]	29/F	Peripheral nerve	Sensorimotor polyneuropathy	(–)	150 mg every 2 days	(+)
Galassi/1984[7]	70/M	Peripheral nerve	Sensorimotor polyneuropathy	Lung	100 mg every 2 days	(+)
	54/M	Peripheral nerve	Sensorimotor polyneuropathy	Lung	High dose	(+)
Okada/1986[8]	25/M	Peripheral nerve Skin	Multifocal sensory neuropathy	Lung/skin/eye	60 mg every 2 days	(+)
Yamane/1986[9]	53/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Lung	40 mg	(–)
Krendel/1992[10]	39/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Skin	40 mg	(+)
Iwata/1993[11]	58/F	Lung	Multifocal sensory neuropathy	Lung/skin/eye	30 mg	(+)
Sharma/1996[12]	40/M	N.A.	Sensorimotor polyneuropathy	Lung/skin/heart	(+)	(+)
	33/M	N.A.	Multifocal motor neuropathy	Lung/skin/eye	(+)	(+)
	48/M	N.A.	Multifocal sensory neuropathy	Lung/lymph node	(+)	(+)
	50/M	N.A.	Multifocal sensory neuropathy	Lung	(+)	(+)
	46/F	N.A.	Multifocal sensory neuropathy	Lung/skin	(+)	(+)
Said/2002[13]	63/M	Peripheral nerve	Multifocal sensorimotor neuropathy	Lung	1 mg/kg	(+)
	69/M	Peripheral nerve	Multifocal sensorimotor neuropathy	(–)	(+)	(+)
Present study	45/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Lung/skin/eye	40 mg	(+)

N.A., not available

compression injury due to resolution of granulomatous lesions.

Sarcoidosis shows a wide variety of clinical features and its diagnosis is difficult in the absence of clinical manifestations such as cutaneous or pulmonary involvement. Any of the preceding neurologic manifestations can occur without any evidence of systemic features of sarcoidosis.[5–7,9,10] It is therefore important to consider the possibility of systemic disease including sarcoidosis even when only peripheral neuropathy is found.

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Vertebral Fracture and Bone Mineral Density in Women Receiving High Dose Glucocorticoids for Treatment of Autoimmune Diseases

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ABSTRACT. ***Objective.*** To evaluate the factors influencing the occurrence of vertebral fracture in patients receiving high dose glucocorticoids (GC).

Methods. A cross-sectional study was performed on women who had received at least 0.5 mg/kg of oral glucocorticoid for the treatment of autoimmune diseases for more than 1 month between 1998 and 2003. Logistic regression analysis and chi-square test were used to examine the effects of glucocorticoid dose and other factors on vertebral fractures. Receiver-operating characteristics curve (ROC) analysis was used to determine the bone mineral density (BMD) cutoff value for the risk of vertebral fracture.

Results. The study population comprised 160 women, including 35 with vertebral fractures. In ROC analysis, the BMD threshold of the risk of fracture for postmenopausal women (0.787 g/cm^2, T score –2.1) was lower than that for premenopausal women (0.843 g/cm^2, T score –1.7). Among patients with fractures, 7 of 16 premenopausal patients had normal BMD values (T score > –1), whereas only one of 19 postmenopausal patients showed a comparable level of BMD. Additionally, vertebral fracture was more frequent for patients with high total cholesterol values (> 280 mg/dl) than for those with normal total cholesterol values (< 220 mg/dl). Moreover, patients with high total cholesterol values had lower BMD values than those with normal total cholesterol values.

Conclusion. The fact that vertebral fracture frequently occurred in premenopausal patients with normal BMD and evidence that hyperlipidemia correlated with fracture suggest the pathology of vertebral fracture secondary to high dose glucocorticoid therapy is multifactorial and possibly involves lipid metabolism. (J Rheumatol 2005;32:863–9)

Key Indexing Terms:

OSTEOPOROSIS	VERTEBRAL FRACTURE	GLUCOCORTICOID
MENOPAUSE	BONE MINERAL DENSITY	HYPERLIPIDEMIA

Glucocorticoids are widely used for the treatment of a variety of autoimmune diseases. Even now, when various novel drugs for the treatment of these diseases are being introduced, glucocorticoids remain the main drugs of choice. However, it has been well established that the use of glucocorticoids can lead to rapid loss of bone mineral density

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(BMD) and to an increased risk of fracture[1]. Several epidemiologic studies have reported a doubling of the risk of hip fracture for users of glucocorticoids[2-4], while large-scale studies have demonstrated a rapid increase in fracture risk following the start of glucocorticoid therapy and a strong correlation of risk with daily glucocorticoid dose[4,5]. Other smaller studies have shown that the cumulative dose, rather than the daily dose, was the more reliable and accurate predictor of fracture[6,7]. When high dose glucocorticoids are used, the loss of bone such as vertebrae can be rapid and lead to vertebral compression fractures within a few months.

Glucocorticoids are also known to affect bone through various pathways, affecting mainly bone formation and, to a lesser extent, bone resorption[8,9]. Findings have been accumulating about the possible role of micro-architectural changes in glucocorticoid induced fracture, although fracture in glucocorticoid users may also occur simply as a result of bone loss. A recent hypothesis is that osteocyte apoptosis is an important factor in deterioration of bone quality and the concomitant rapid increase in the risk of fracture[10]. In addition, there is a report that glucocorticoid users with fracture had considerably higher BMD than patients with fracture due to primary osteoporosis[11]. These reports support the notion that a non-BMD-related mechanism may also be responsible for inducing fracture in users of glucocorticoids[12].

We conducted a multicenter, cross-sectional analysis, specifically investigating high dose glucocorticoid users treated for autoimmune diseases, to determine the BMD cutoff value for the risk of vertebral fracture, and to examine the correlation between glucocorticoid induced vertebral fracture or loss of BMD and multiple factors including menopause, glucocorticoid dose, and other glucocorticoid induced secondary complications.

MATERIALS AND METHODS

Study population of glucocorticoid users. Data on 160 Japanese women, aged 16–85 years and treated with glucocorticoids for autoimmune diseases, were collected from the rheumatology departments of 11 institutions that joined the Research Committee for Glucocorticoid-Induced Osteoporosis organized by the Japanese Ministry of Health, Labor and Welfare. This study was limited to patients who had been receiving oral glucocorticoid therapy (mean daily dose 0.5 mg/kg prednisone or equivalent) for at least 1 month between April 1998 and March 2003. The basic clinical data including risk factors and dose and duration of glucocorticoid therapy were collected retrospectively by treating physicians in reference to medical records from each institution, and the collected data were reviewed by the central committee for selecting eligible patients. As for treatment or prevention of osteoporosis, there were no restrictions for enrollment of patients based on protocols for the use of bisphosphonates, calcium, vitamin D, or other antiresorptive drugs. Diseases they were treated for included systemic lupus erythematosus (SLE; 79 cases), Sjögren's syndrome (15 cases), polymyositis (13 cases), mixed connective tissue disease (12 cases), adult onset Still's disease (8 cases), polymyalgia rheumatica (7 cases), dermatomyositis (6 cases), systemic sclerosis (5 cases), and others (15 cases). Patients with rheumatoid arthritis were excluded from this study.

BMD of the patients was assessed for the lumbar spine (L2–L4), femoral neck, and radial head by means of dual-energy x-ray absorptiometry (DEXA). Since the DEXA machines used for the measurement of BMD differed from hospital to hospital, the raw BMD values were converted to comparable values for the QDR-2000 (Hologic Inc., Waltham, MA, USA) as described[13]. High dose glucocorticoid therapy was defined as a mean daily dose > 0.5 mg/kg of prednisone or equivalent dose of other glucocorticoids for at least 1 month.

Vertebral fracture was confirmed radiologically by lateral radiographs of the thoracolumbar spine with the method established by Orimo, *et al*[14]; the presence of vertebral fracture was semiquantitatively confirmed if either the ratio of middle/anterior or middle/posterior height of a vertebral body was < 0.8, or the ratio of anterior/posterior height of a vertebral body was < 0.75. The judgment of fracture was double-checked by 2 examiners in each institution. If BMD was measured more than once in the same patient, the last BMD value was adopted for patients without vertebral fracture, and for patients with fracture, the BMD measured at the timepoint nearest the radiological confirmation of initial vertebral fracture was used.

The daily, cumulative, and maximum glucocorticoid doses, and the total duration (in days) of prior glucocorticoid therapy were also entered into the analysis. Clinical factors that may affect the occurrence of vertebral fracture, comprising age, body mass index (BMI), menopause, BMD (T scores), hypertension, total cholesterol, and HbA1c were evaluated. Diagnoses for hypertension and diabetes mellitus were determined according to American Heart Association[15] and American Diabetes Association[16] guidelines, respectively. Hyperlipidemia was diagnosed according to the criteria of the Japanese Atherosclerosis Society[17], in which total cholesterol level > 220 mg/dl is regarded as hyperlipidemia.

Statistical analysis. Logistic regression analysis was used to calculate the influence of various variables on vertebral fracture including age, BMI, menopause, BMD, and glucocorticoid related parameters. For determination of BMD cutoff values to identify women with vertebral fracture, sensitivity, specificity, and BMD cutoff values were calculated using receiver-operating characteristics curve (ROC) analysis. As for patients with vertebral fracture, the chi-square test was used to determine the difference in BMD between premenopausal and postmenopausal glucocorticoid users. P values < 0.05 were deemed to be statistically significant. The MedCalc statistical analysis software package (MedCalc Software, Mariakerke, Belgium) was used for statistical analyses.

RESULTS

Variables affecting vertebral fracture in high dose glucocorticoid users. For this study, 160 patients were assessed. The baseline information of enrolled patients is shown in Table 1. BMD values of this group negatively correlated with patients' age ($p < 0.001$, $r = -0.366$). A logistic regression analysis of patients with vertebral fracture (fracture group) and those without vertebral fracture (non-fracture group) is presented in Table 2. The respective mean BMD values of the fracture group (35 cases; 19 postmenopausal, 16 premenopausal) and the non-fracture group (125 cases) were 0.781 and 0.871 g/cm^2 ($p = 0.004$). There was a significant difference between the 2 groups in BMI and BMD, but no difference in age, ratio of menopause, and total glucocorticoid dose, as shown in Table 2. The logistic regression analyses including the other glucocorticoid related variables such as cumulative days of glucocorticoid use, mean glucocorticoid dose (daily), cumulative glucocorticoid dose, and maximal glucocorticoid dose showed no significant difference between the 2 groups (data not shown). The mean daily glucocorticoid dose for premenopausal women (age 34.9 ± 9.4 yrs) was 16.4 ± 16.5 mg/day and for postmenopausal

Table 1. Baseline characteristics of 160 patients in the study.

	Premenopausal	Postmenopausal	Total	p
Age, yrs, mean ± SD	34.9 ± 9.4	62.6 ± 9.9	47.9 ± 16.9	< 0.05
BMI, kg/m^2	21.7 ± 14.1	22.0 ± 3.5	21.9 ± 3.6	NS
BMD, g/cm^2	0.926 ± 0.149	0.767 ± 0.149	0.852 ± 0.168	< 0.05
Daily prednisolone dose*, mg/day	16.4 ± 16.5	10.7 ± 9.9	13.7 ± 14.1	< 0.05
Cumulative dose of prednisolone*, g	17.1 ± 31.3	8.2 ± 10.4	12.8 ± 24.0	NS
Duration of glucocorticoid treatment, days	1993.1 ± 2091.9	2069.9 ± 2317.4	2027.8 ± 2189.4	NS

* Adjusted to the dose equivalent to prednisolone. NS: not significant.

Table 2. Logistic regression analysis of treatment related variables and vertebral fracture in high dose user of glucocorticoid.

	Vertebral Fracture			
	Yes	No	Z	p
Age, yrs, mean ± SD	50.7 ± 3.2*	47.1 ± 1.4	0.5925	0.554
Menopause (%)	19/35 (54.3)	56/125 (44.8)	0.270	0.787
BMI	22.4 ± 0.8	21.8 ± 0.3	1.961	< 0.05
BMD, L2–4, g/cm^2	0.781 ± 0.033	0.871 ± 0.014	2.218	< 0.03
Total glucocorticoid dose*, g	24.3 ± 6.6	22.2 ± 4.4	0.789	0.430

* Adjusted to the dose equivalent to prednisolone.

women (age 62.6 ± 9.9 yrs) 10.7 ± 9.9 mg/day ($p < 0.05$). Compared to postmenopausal glucocorticoid users, premenopausal glucocorticoid users had significantly higher average BMD (L2–L4) in the lumbar spine, femoral neck, and radial head (data not shown).

For postmenopausal women, the mean BMD value of the fracture group was significantly lower than that of the non-fracture group ($p < 0.01$), as shown in Figure 1. In contrast, there was no significant difference in BMD values between the fracture group and non-fracture group among premenopausal women. Of special interest is that 7 of the 16 premenopausal patients (43.7%) in the fracture group showed normal values (T score > –1), whereas only one of the 19 postmenopausal patients (5.3%) did ($p < 0.01$). There was no statistically significant difference between the fracture group and non-fracture group for maximum glucocorti-

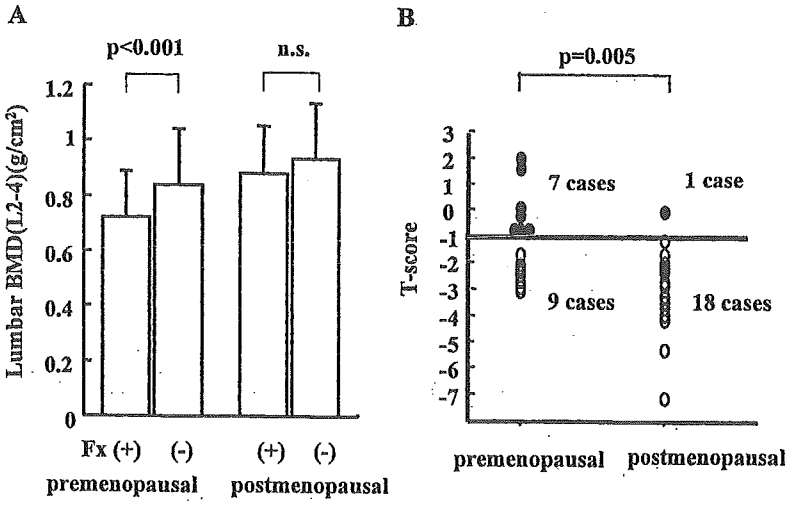

Figure 1. (A) Lumbar BMD from fracture (Fx) and non-fracture patient groups taking high dose glucocorticoids. There were significant differences in lumbar BMD between fracture and non-fracture groups in premenopausal women ($p < 0.001$), whereas no difference was detected between the 2 groups in postmenopausal women. ns: not significant. (B) T scores from premenopausal or postmenopausal women with vertebral fracture. Premenopausal glucocorticoid users frequently incurred vertebral fracture even when BMD was not reduced (T > –1) compared with postmenopausal women ($p = 0.005$). ●: fracture patients whose T scores were not reduced.

coid dose, mean daily glucocorticoid dose, disease background, and history of methylprednisolone pulse therapy in premenopausal women (data not shown).

BMD cutoff values for vertebral fracture in glucocorticoid users assessed by ROC analysis. ROC analysis was used to determine the BMD cutoff level for vertebral fracture in high dose glucocorticoid users. The cutoff values were defined as the values that proved to be effective for the sensitive and specific differentiation of subjects with and without vertebral fracture. As shown in Figure 2, the cutoff values for the risk of vertebral fracture for premenopausal, postmenopausal, and total patients were 0.843, 0.787, and 0.787 g/cm^2, respectively.

Hyperlipidemia correlates with BMD value and vertebral fracture. The influence of common glucocorticoid induced complications such as hyperlipidemia, diabetes mellitus, and hypertension on vertebral fracture were not entered into the logistic regression analysis, since those variables are not recognized as independent to glucocorticoid dose-related variables. Table 3 shows that hyperlipidemia has negative correlation with BMD, while HbA1c level did not correlate with BMD values. Nor did hypertension correlate with the level of BMD (data not shown). Then we compared patients with normal total cholesterol (< 220 mg/dl) value to those with above-normal values for further analysis. The peak value of total cholesterol after initiation of glucocorticoid therapy was used for the analysis in each patient. When we raised the comparative total cholesterol level to > 280 mg/dl, patients with high total cholesterol (> 280 mg/dl) value had lower BMD (p = 0.016) and higher risk of vertebral fracture (relative risk 3.1, p = 0.032) than those with normal total cholesterol level (Figure 3). These results suggest that hyperlipidemia following high dose glucocorticoid therapy may contribute to the risk for BMD reduction and vertebral fracture.

DISCUSSION

High dose glucocorticoid therapy is often the first choice for patients with autoimmune diseases, such as SLE, that frequently affect premenopausal women. Although the efficacy of bisphosphonate has recently been reported in high dose glucocorticoid users[18], there is only limited knowledge of the clinical risk factors for secondary osteoporosis occurring in high dose glucocorticoid users. This is the first extensive study focusing on the relationship of vertebral fracture and BMD in patients with high dose glucocorticoid therapy. We observed unique effects of high dose glucocorticoid therapy: First, the BMD cutoff value for the risk of vertebral fracture applicable to premenopausal glucocorticoid users was higher than that applicable to postmenopausal glucocorticoid users. Second, premenopausal glucocorticoid users, even with normal BMD values, were found to frequently incur vertebral fracture. Third, hyperlipidemia significantly correlated with vertebral fracture and low BMD.

ROC analysis showed that the BMD cutoff value for the risk of vertebral fracture for premenopausal women was 0.843 (T score = −1.7) and for postmenopausal women 0.787 (T score = −2.1). These cutoff values lie between 70% (T score = −2.6) and 80% (T score = −1.7) of the young adult

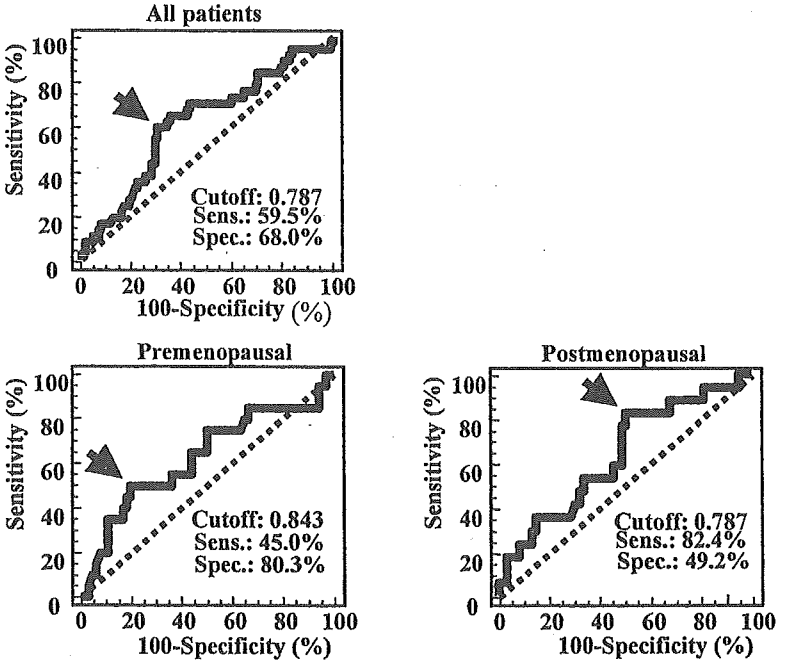

Figure 2. ROC analysis of lumbar BMD values for all patients, premenopausal and postmenopausal patients with vertebral fracture treated with high dose glucocorticoid. Arrows indicate cutoff points. Sens: sensitivity; Spec: specificity.

Table 3. The relationship between other glucocorticoid related complications and BMD or vertebral fracture in high dose glucocorticoid users (chi-square test).

Vertebral Fracture	Yes	No	p
Diabetes mellitus	26	134	
HbA1c, mg/dl*	7.68 ± 1.93	5.15 ± 0.66	< 0.01
BMD, g/cm^2	0.858 ± 0.149	0.850 ± 0.17	NS
Vertebral fracture, yes/no (%)	5/21 (19.2)	29/105 (21.6)	NS
Hyperlipidemia (cases)	95	65	
Total cholesterol, mg/dl*	283.2 ± 54.8	207.8 ± 23.0	< 0.01
BMD, g/cm^2	0.834 ± 0.176	0.876 ± 0.173	0.03
Vertebral fracture, yes/no (%)	23/72 (24.2)	11/54 (16.9)	NS

* Peak values after glucocorticoid therapy are shown. Patients whose value was > 220 mg/dl was defined to have hyperlipidemia. NS: not significant.

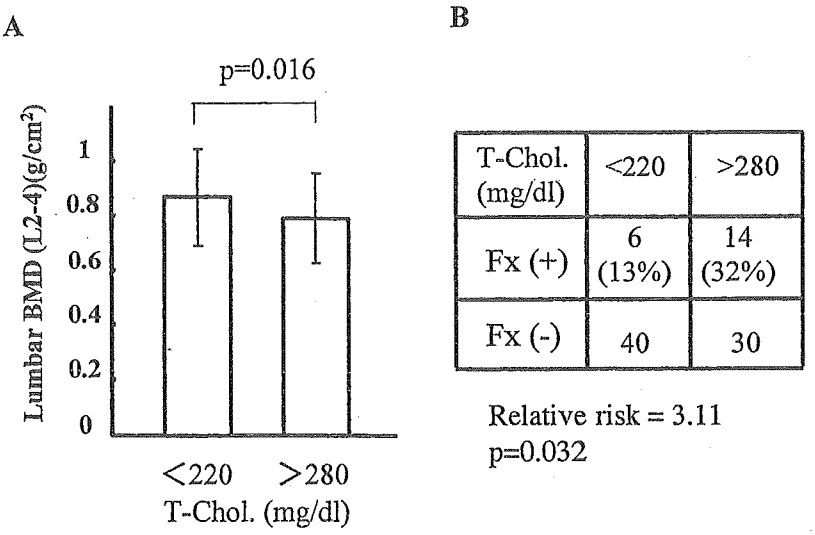

Figure 3. Influence of hyperlipidemia on lumbar BMD and vertebral fracture (Fx) in high dose glucocorticoid users. (A) Comparison of lumbar BMD between patients with high (> 280 mg/dl) and with normal (< 220 mg/dl) total cholesterol (T-Chol) values. (B) Comparison of the ratio of vertebral fracture between patients with high (> 280 mg/dl) and with normal (< 220 mg/dl) total cholesterol values. Chi-square analysis revealed that vertebral fracture was more frequent in patients with high total cholesterol level than in those with normal level (relative risk = 3.11, p = 0.032).

mean value of a large-scale Japanese study of primary osteoporosis by Orimo, *et al*, in which the cutoff value for osteoporosis was determined to be 70% of young adult mean[14]. There have been arguments about the difference of BMD threshold for fractures between postmenopausal users of glucocorticoids and nonusers. There are reports showing the BMD distribution of patients with vertebral fractures was similar for glucocorticoid users and nonusers[19,20]. On the other hand, other studies found that postmenopausal women taking glucocorticoids had a higher risk of fracture compared with nonusers, even at comparable levels of BMD[11,21]. Although our study was not designed to address this controversy, the relatively high BMD cutoff value, 80% of the young adult mean, for premenopausal women established in our study suggests that BMD alone may not be sufficient for predicting the risk of vertebral fracture for premenopausal users of glucocorticoids.

This notion is supported by our finding that premenopausal glucocorticoid users frequently experienced complications of vertebral fracture even when they registered normal BMD values. Vertebral fracture was seen in as many as 43% of premenopausal glucocorticoid users even when their BMD values were not particularly low (T score > −1). Recent guidelines from Europe and North America have been developed to establish intervention thresholds for glucocorticoid induced osteoporosis in patients with high BMD levels[22,23] or regardless of BMD level[24]. The recent guidelines of the American College of Rheumatology advocate intervention for all patients whose therapy calls for use of > 5 mg/day glucocorticoid for at least 3 months, and for

patients on a longterm glucocorticoid regimen with a BMD below a T score of –1.0[22]. Guidelines from the UK advocate an intervention threshold at a T score of –1.5 for patients who are scheduled to be given > 7.5 mg/day glucocorticoid for at least 6 months[23]. Our results suggest the need for developing a new therapeutic approach to prevent glucocorticoid induced osteoporosis in addition to starting antiresorptive therapy at high BMD thresholds.

Accumulating findings indicate that BMD is not the only factor that affects the risk of vertebral fracture[1,12,25]. One mechanism for the rapid onset of fracture risk could be osteocyte apoptosis, which leads to a deterioration of bone quality and a rapid increase in fracture risk[10]. Osteocyte apoptosis is prevalent in glucocorticoid induced osteoporosis[26]. The network of osteocytes is thought to detect microdamage to bone and be involved in bone repair remodeling. Therefore, osteocyte apoptosis together with glucocorticoid induced suppression of osteoblast generation could lead to growing micro-damage and a resultant increase in bone fragility. Thus, it is important to develop a new method to estimate bone fragility besides BMD measurement.

Another candidate factor that may contribute to the risk of osteoporosis from our study is hyperlipidemia. Our results showed that high total cholesterol (> 280 mg/dl) may be a risk factor for low BMD and vertebral fracture. There are reports of *in vitro* studies suggesting that low density lipoprotein oxidation products could promote osteoporosis by inhibiting osteoblast differentiation and by directing progenitor marrow stroma cells to undergo adipogenic instead of osteogenic differentiation[27,28]. Although these *in vitro* studies imply the possible involvement of lipid metabolism in the process of osteoporosis, there has been no report confirming the relationship of hyperlipidemia and glucocorticoid induced osteoporosis, and many clinical trials examining the efficacy of HMG-CoA reductase in preventing osteoporosis have had negative results. Therefore, further investigation is needed to establish a therapeutic strategy for preventing glucocorticoid induced osteoporosis in patients with hyperlipidemia.

Some reports stress the importance of daily glucocorticoid dose (mean) over cumulative glucocorticoid dose as an effective predictor of fracture[4,5,11], while others stress cumulative rather than daily glucocorticoid dose[6,7]. We detected no statistically significant difference between the occurrence of fracture and the mean daily glucocorticoid dose ($p = 0.483$) or cumulative glucocorticoid dose ($p = 0.794$), probably because of the limitation of our cross-sectional study and the limited numbers of patients with fracture. An important factor affecting our results may be differences in the use of antiresorptive drugs, especially bisphosphonates. This may be due partly to the Japanese legislative environment, since prophylactic use of drugs has not been allowed yet in the Japanese health insurance system. As this is a cross-sectional study, there are some limitations to interpreting our results. The onset of vertebral fracture is not predictable in prevalent fracture cases, and in these cases the influence of BMD may be different from that in incident fracture cases. To address these questions, we are now conducting a randomized cohort trial on patients who start glucocorticoid administration at a high dose, > 0.5 mg/kg.

Our findings support the hypothesis that treatment with glucocorticoids influences the occurrence of vertebral fracture by means of a mechanism independent of BMD. Moreover, it will be necessary to develop a new approach to assess and reduce the risk of vertebral fracture in premenopausal users of glucocorticoids.

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Autoantibodies to a 140-kd Polypeptide, CADM-140, in Japanese Patients With Clinically Amyopathic Dermatomyositis

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Objective. **To identify novel autoantibodies specific for dermatomyositis (DM), especially those specific for clinically amyopathic DM (C-ADM).**

Methods. **Autoantibodies were analyzed by immunoprecipitation in 298 serum samples from patients with various connective tissue diseases (CTDs) or idiopathic pulmonary fibrosis (IPF). Antigen specificity of the sera was further examined by immunoblotting and indirect immunofluorescence (IF). The disease specificity and clinical features associated with the antibody of interest were determined.**

Results. **Eight sera recognized a polypeptide of ~140 kd (CADM-140 autoantigen) by immunoprecipitation and immunoblotting. Immunoreactivity was detected in the cytoplasm, and indirect IF revealed a granular or reticular pattern. Anti–CADM-140 antibodies were detected in 8 of 42 patients with DM, but not in patients with other CTDs or IPF. Interestingly, all 8 patients with anti–CADM-140 antibodies had C-ADM. Among 42 patients with DM, those with anti–CADM-140 autoantibodies had significantly more rapidly progressive interstitial lung disease (ILD) when compared with patients without anti–CADM-140 autoantibodies (50% versus 6%; $P = 0.008$).**

Conclusion. **These results indicate that the presence of anti–CADM-140 autoantibodies may be a novel marker for C-ADM. Further attention should be directed to the detection of rapidly progressive ILD in those patients with anti–CADM-140 autoantibodies.**

Polymyositis (PM)/dermatomyositis (DM) is a chronic inflammatory disorder that culminates in injury to the skin and muscle and, sometimes, is associated with interstitial lung disease (ILD) and/or neoplasia (1,2). A number of autoantibodies are associated with myositis, including those specific for aminoacyl–transfer RNA synthetase (anti-ARS) (3), signal recognition particle (anti-SRP) (4), and Mi-2 (5). These autoantibodies have proven to be clinically useful in the diagnosis and classification of these diseases and are predictive of responses to treatment.

It has been known for some time that certain patients may have the typical skin manifestations of DM but no evidence of myositis, a condition known as amyopathic DM. Recently, Sontheimer proposed the existence of a unique subgroup of patients with DM who have the clinical cutaneous features of DM but no evidence of clinical myositis symptoms for at least 2 years after the onset of skin manifestations (referred to as clinically amyopathic DM [C-ADM]) (6). In other words, C-ADM includes patients with amyopathic DM and patients with hypomyopathic DM (patients with subclinical signs of myositis and DM skin manifestations). Some patients with C-ADM, especially those in Japan (7), have been noted to develop rapidly progressive ILD. This condition in many of these patients is resistant to treatment, and fatal outcomes have been observed.

Because of the severity of ILD accompanying C-ADM, a marker autoantibody would be useful for early diagnosis and treatment monitoring. Potential marker autoantibodies have been described by Targoff et al, who, in a preliminary study, described specificity for a 95-kd Se protein, as well as an unidentified 155-kd protein (8). However, a full survey of the autoantibodies

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associated with C-ADM has not been performed. In the present study, we examined the sera from 15 Japanese patients with C-ADM to identify additional autoantibodies associated with this disease.

PATIENTS AND METHODS

Patients and sera. Serum samples were obtained from 255 randomly selected Japanese adult patients with connective tissue diseases (CTDs) who were being followed up in clinics at Keio University in Tokyo and collaborating medical centers. These sera were obtained, prior to therapy, from a cohort of 61 patients with PM, 42 with DM (including 15 with C-ADM), 50 with rheumatoid arthritis, 46 with systemic lupus erythematosus, 27 with mixed CTD/overlap syndrome, 22 with systemic sclerosis, and 7 with Sjögren's syndrome. Sera from 43 patients with idiopathic pulmonary fibrosis (IPF) and 16 normal human sera were used as control sera. The diagnosis of C-ADM was based on diagnostic criteria proposed by Sontheimer (6), i.e., DM patients with no clinical muscle symptoms for more than 2 years after the onset of skin manifestations.

The patients were diagnosed as having ILD according to the results of chest radiography, chest computed tomography (CT), and pulmonary function testing, which included the percent predicted values for forced vital capacity and diffusing capacity for carbon monoxide. A subset of patients with rapidly progressive ILD was defined as those presenting with progressive dyspnea and progressive hypoxemia, and a worsening of interstitial change on the chest radiograph within 1 month from the onset of respiratory symptoms.

Immunoprecipitation. The immunoprecipitation assay was performed using extracts of the leukemia cell line, K562, as previously described (9). A total of 10 μl of patient serum was mixed with 2 mg of polypeptide A–Sepharose CL-4B (Pharmacia Biotech AB, Uppsala, Sweden) in 500 μl of immunoprecipitation buffer (10 m*M* Tris HCl, pH 8.0, 500 m*M* NaCl, 0.1% Nonidet P40) and incubated for 2 hours at 4°C, and then washed 3 times with immunoprecipitation buffer.

For polypeptide studies, antibody-coated Sepharose beads were mixed with 100 μl of ^{35}S-methionine–labeled K562 cell extracts derived from 2×10^5 cells, and rotated at 4°C for 2 hours. After 6 washes, the Sepharose beads were resuspended in sodium dodecyl sulfate (SDS) sample buffer and the polypeptides were fractionated by 6% SDS–polyacrylamide electrophoresis gels. Radiolabeled polypeptide components were analyzed by autoradiography.

For analysis of RNA, the antigen-bound Sepharose beads were incubated with 100 μl of K562 cell extracts (6×10^6 cell equivalents per sample) for 2 hours at 4°C. To extract bound RNA, 30 μl of 3.0*M* sodium acetate, 30 μl of 10% SDS, 2 μl of carrier yeast transfer RNA (10 mg/ml; Sigma, St. Louis, MO), and 300 μl of phenol:chloroform:isoamyl alcohol (50:50:1, containing 0.1% 8-hydroxyquinoline) were added. After ethanol precipitation, the RNA was resolved using a 7*M* urea–10% polyacrylamide gel, which was subsequently silver-stained (Bio-Rad, Hercules, CA).

Immunoblotting. Immunoblotting analysis was performed using K562 cell extracts in a modification of the procedure described by Towbin et al (10).

Immunodepletion. A 10-μl aliquot of the prototype serum of autoantibodies to the 140-kd polypeptide was mixed with 2 mg of Sepharose beads and incubated for 2 hours at 4°C, followed by 3 washes with immunoprecipitation buffer. Another serum that recognized the 140-kd polypeptide was added in a dose-dependent manner (0 μl, 10 μl, 25 μl, and 50 μl) and then incubated. After 3 washes, immunoprecipitation for polypeptide analysis was performed as described above.

Indirect immunofluorescence (IF). Indirect IF was performed using HEp-2 cells and fluorescein-labeled anti-human immunoglobulin (Inova Diagnostics, San Diego, CA).

Clinical studies. The patients whose sera immunoprecipitated a 140-kd polypeptide were examined for their clinical symptoms, clinical course, muscle enzyme levels (creatine kinase [CK] and aldolase), results on chest radiographic and CT scans, and findings of skin pathology. An assessment of muscle weakness was performed using a manual muscle test (11). Some patients were also examined by electromyogram and muscle magnetic resonance imaging (MRI), and by pathologic analysis of the muscle.

Statistical analysis. The 2 groups of DM patients with or without autoantibodies to the 140-kd polypeptide were compared. The results of comparisons between groups were analyzed using the chi-square test, with Yates' correction where appropriate.

RESULTS

Detection of anti–140-kd polypeptide antibodies in patients with C-ADM. We screened 298 patient sera and 16 normal human sera by immunoprecipitation. Sera from 8 (19%) of 42 patients with DM immunoprecipitated a polypeptide of ~140 kd from ^{35}S-methionine–labeled K562 cell extracts (Figure 1A, lanes 1–8). All 8 patients were diagnosed as having C-ADM, a subtype of DM. In the analysis of RNA specificity, these sera did not immunoprecipitate any nucleic acid band, except for 1 patient's serum, which precipitated hYRNA of SSA/Ro components.

The C-ADM sera that immunoprecipitated the 140-kd polypeptide were also used to immunoblot K562 cell extracts. These sera from C-ADM patients displayed a similar reaction on immunoblot, with a polypeptide band of similar molecular weight (results not shown).

For identification of novel autoantibodies recognizing the 140-kd molecule, the polypeptide immunoprecipitated by the prototype serum was compared with antigens of similar molecular weight recognized by other known autoantibodies (Figure 1B). The protein recognized by the prototype serum migrated slightly faster than the 140-kd protein recognized by anti-MJ antibody (Figure 1B, lane 2) and faster than that recognized by anti–RNA helicase A antibody (Figure 1B, lane 3), but more slowly than the 120-kd protein precipitated by